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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,796	12/16/2002	Paul Keown	UBC-0003	7651

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,796	KEOWN ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/06/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 16, 2002. Currently, claims 24-55 are pending.

Priority

2. This application claims priority to two foreign filed applications; 371 of PCT/CA00/01043, filed September 8, 2000 and provisional application 60/160,618, filed October 20, 1999. The first line of the specification does not reference either the provisional application or the benefit of 371. See 201.11 MPEP.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Drawings

3. The drawings are acceptable.

Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

There are numerous sequences listed throughout the specification, page 4, 5, 11, for example which are not identified by SEQ ID NO:. Further, there is no Sequence listing in the instant application. Appropriate correction is required.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 24, 29-44, 48-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of diagnosis by identifying a polymorphism in the interferon gamma gene.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

With respect to claims which encompass allelic variations. As provided in Example 11, no common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, "a polymorphism in the interferon gamma gene" alone is insufficient to describe the genus. There is no description of the

mutational sites that exist in nature and there is no description of how the structure of "a polymorphism in the interferon gamma gene" relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning variants does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 24-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 24-55 are drawn to a method of diagnosis comprising identifying a patient at risk of an arthritis, the patient having an interferon gamma gene, and testing the patient to characterize a polymorphism in the interferon gamma gene.

The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification and Working Examples

The instant specification provides the various alleles which have been identified in the CA dinucleotide repeat of IFNG located in intron 1 (page 5). The specification teaches analyzing 48 Caucasian patients with severe RA; 39 patients with mild RA and 50 patients that did not provide symptoms (page 10). As seen in Table 1, A4 and A6 appear to be associated with RA.

The unpredictability of the art and the state of the prior art

The art, both prior and postfiling date, teaches the lack of association between a dinucleotide repeat polymorphism in the IFNG gene.

John et al. (Ann Rheum. Dis. Vol. 57, pages 361-365, June 1998) teaches an analysis of cytokine genes to rheumatoid arthritis. As seen in Table 1, the dinucleotide repeat marker of IFNG, at 12q24.1 in intron 1, has been analyzed. The primers of Table 2 flank the dinucleotide repeat region taught in the instant specification. As seen in Table 4, none of the IFNG markers have a significant p-value for RA in early or late-onset, for example. John teaches that the analysis did not support an association with both IFN-gamma allele and RA. John provides several possible explanations including polymorphic microsatellites with many alleles (page 365, col. 1).

Ollier et al. (Lancet, Vol. 356, pages 783-784, September 2000) reviews the study by the instant inventors which was published in the same volume of the Lancet, page 820. Ollier cautions the results obtained. Ollier states that association studies are prone to generating false-positive associations and the literature is littered with reports of associations that cannot be replicated. Ollier cautions the findings of Khani-Hanjani and colleagues to be replicated independently in data sets of sufficient size to provide adequate statistical power. Ollier notes that spurious associations can occur when inappropriate matching of cases and controls causes population stratification. Ollier teaches that microsatellite alleles are technically more difficult to assign in association studies than in family studies and care must be taken to avoid "allele slippage". Ollier reviews that another study by John which provided no evidence for linkage with IFNG was observed in the total data set (page 784, col. 1). Ollier cautions the results of Khani-Hanjani until independently confirmed by other analyses.

Pokorny et al. (The Lancet, Vol. 358, pages 122-123, July 14, 2001) teaches that no association between interferon-gamma microsatellite and rheumatoid arthritis could

be confirmed. Pokorny teaches the analysis was performed in Caucasian patients with RA and healthy blood donors. Pokorny teaches that no 120 or 122 bp microsatellite alleles were detected amongst any of the patients or controls and that non of the interferon gamma microsatellite alleles was associated with either the incidence or the severity of RA. Pokorny teaches that using this independent data set was unable to confirm an association between RA and its severity and the IFNG intron A 126 bp microsatellite allele. Pokorny teaches that it is possible that the differences between the earlier study of Khani-Hanjani and the instant study are due to technical issues with the earlier study or to characteristics of the patient pool. Pokorny concludes that no evidence was found to support the effect reported by Khani-Hanjani.

Constantin et al. (The Lancet, Vol. 358, pages 2051-2052, December 15, 2001) teaches their study failed to confirm the association between the IFNG gene polymorphism and RA susceptibility or severity. Constaintin investigated the association in French patients (page 2051, col. 1). As seen in Table 1, no association exists between the 122 or the 126 allele. Constantin acknowledges that the allele carriage rates recorded were more in line with the previously reported healthy German, Swedish, British and Sardinian individuals.

Vandenbroeck et al. (Arthristi & Rheumatism, Vol. 48, pages 2773-2778, October 2003) teaches polymorphisms in the interferon-gamma gene may be sex-based differential susceptibility. Vandenbroeck, in Table 1, fails to illustrate any IFNG, CA markers which are associated with RA.

Miterski et al. (BMC Genetics, Vol. 5, No. 2, pages 1-14, February 2004) teaches that none of the investigated genetic markers are associated with RA or JRA. Figure 5, page 8, illustrates frequency of alleles in controls, RA and JRA patients. Miterski

teaches that no differences in the distribution of alleles was found between patients and controls and that the role of IFNG in RA susceptibility is not clear today (page 11).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of negative teachings which would have to be studied to determine the differences between the instant study and the studies found in the art to distinguish the discrepancies. The prior art enumerates numerous criticisms of the Khani-Hanjani study which reported significant and strong association of an intronic microsatellite marker in the IFNGB gene with rheumatoid arthritis. The art provides direct comparisons to the study of Khani-Hanjani and suggests the possible allele slippage, lack of replicability, difficulty of microsatellite marker associations, small samples, characteristics of the patient pool, assignment of disease as severe or mild disease based on treatment, for example.

Additionally, the claims are broadly drawn to "a polymorphism" (Claims 24, for example). The instant specification has provided only a single polymorphism which has been studied and analyzed with respect to RA. As seen in the art, association studies are highly unpredictable and require careful analysis and review. It is unpredictable whether additional polymorphisms within the IFNG gene would be associated in a predictable manner with arthritis. While one could conduct additional experimentation to determine whether additional polymorphisms existed in the IFNG gene then determine whether these polymorphisms might be associated with arthritis, the outcome of such research cannot be predicted and such further research and experimentation are both unpredictable and undue.

This would require much inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the prior art and the post filing date art does not support the analysis provided in the instant specification, it is unpredictable whether the IFNG dinucleotide repeat is associated with RA in a replicable manner. The art analyzed RA and JRA patients and is unable to determine an association. The art analyzed Caucasians, French as well as frequencies from German, Swedish, British and Sardinian individuals. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized non association. The art provides direct comparisons to the study of Khani-Hanjani and suggests the possible allele slippage, lack of replicability, difficulty of microsatellite marker associations, small samples, characteristics of the patient pool, assignment of disease as severe or mild disease based on treatment, for example. The prior art and the art have provided not confirmation of the instant study and has only provided that no association could be confirmed. It is unpredictable whether the skilled artisan would be able to reliable use the dinucleotide repeat to diagnose a patient with arthritis since no studies have confirmed the association. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided

in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 24-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 24-55 are indefinite because it is unclear as to whether the claims are intended to be limited to method of diagnosing or whether the claims are intended to be limited to methods of testing a patient to characterize a polymorphism in the IFNG gene. The claims are drawn to a method of diagnosing. However, the final step is one of testing the patient to characterize a polymorphism in the interferon gamma gene. Accordingly, it is unclear whether the method requires diagnosis or whether the claimed method is one for testing the patient for a polymorphism.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 24-30, 32-34, 43-49, 51-55 are rejected under 35 U.S.C. 102(b) as being anticipated by John et al. (Ann Rheum. Dis. Vol. 57, pages 361-365, June 1998).

The claims currently require a method of diagnosis, but fail to provide a step within the claimed methods which requires diagnosis (see 112/2nd) thus, the instant rejection applies to a broad interpretation of the instant claims.

John teaches an analysis of cytokine genes to rheumatoid arthritis. As seen in Table 1, the dinucleotide repeat marker of IFNG, at 12q24.1 in intron 1, has been analyzed. The primers of Table 2 flank the dinucleotide repeat region taught in the instant specification. As seen in Table 4, none of the IFNG markers have a significant p-value for RA in early or late-onset, for example. John teaches that the analysis did not support an association with both IFN-gamma allele and RA. John provides several possible explanations including polymorphic microsatellites with many alleles (page 365, col. 1). John teaches each and every step of the claimed method. Patients with RA were identified and the IFNG gene was analyzed for a dinucleotide repeat using the published primers in intron 1. the patient was tested to characterize the polymorphism in the IFNG gene. Thus, John teaches every limitation of the instant claims.

Conclusion

10. No claims allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Patent Examiner
January 9, 2005